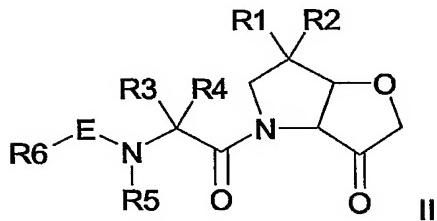


Claims

A compound of the formula II



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wherein

one of R<sup>1</sup> and R<sup>2</sup> is halo and the other is H or halo;

R<sup>3</sup> is C<sub>1</sub>-C<sub>5</sub> straight or branched chain, optionally fluorinated, alkyl;

R<sup>4</sup> is H; or

10 R<sup>3</sup> together with R<sup>4</sup> defines

a spiro-C<sub>5</sub>-C<sub>7</sub> cycloalkyl, optionally substituted with 1 to 3 substituents selected from halo, hydroxyl, C<sub>1</sub>-C<sub>4</sub> alkyl or C<sub>1</sub>-C<sub>4</sub> haloalkyl; or optionally bridged with a methylene group; or

a C<sub>4</sub>-C<sub>6</sub> saturated heterocycle having a hetero atom selected from

15 O, NR<sub>a</sub>, S, S(=O)<sub>2</sub>;

R<sup>5</sup> is independently selected from H or methyl;

E is -C(=O)-, -S(=O)<sub>m</sub>-, -NR<sup>5</sup>S(=O)<sub>m</sub>-, -NR<sup>5</sup>C(=O)-, -OC(=O)-,

20 R<sup>6</sup> is a stable, optionally substituted, monocyclic or bicyclic, carbocycle or heterocycle wherein the or each ring has 4, 5 or 6 ring atoms and 0 to 3 hetero atoms selected from S, O and N and wherein the optional substituents comprise 1 to 3 members selected from R<sub>7</sub>;

R<sub>7</sub> is independently selected from halo, oxo, nitrile, nitro, C<sub>1</sub>-C<sub>4</sub> alkyl, -XNR<sub>a</sub>R<sub>b</sub>, -XNR<sub>b</sub>R<sup>9</sup>, -NR<sub>b</sub>C<sub>1</sub>-C<sub>4</sub>alkylR<sup>9</sup>, NH<sub>2</sub>CO-, X-R<sup>9</sup>, X-O-R<sup>9</sup>, O-X-R<sup>9</sup>, X-C(=O)R<sup>9</sup>, X-(C=O)NR<sub>a</sub>R<sup>9</sup>, X-NR<sub>b</sub>C(=O)R<sup>9</sup>, X-NHSO<sub>m</sub>R<sup>9</sup>, X-S(=O)<sub>m</sub>R<sup>9</sup>, X-C(=O)OR<sup>9</sup>, X-

25 NR<sub>b</sub>C(=O)OR<sup>9</sup>;

R<sub>9</sub> is independently H, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, pyranyl, thiopyranyl, furanyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, phenyl, any of which is optionally substituted with R<sup>10</sup>;

$R_{10}$  is independently selected from hydroxy,  $XR^9$ ,  $-XNRaRb$ ,  $-XNRbR^9$ ,  $-NRbC_1-C_4alkylR^9$ , nitro, cyano, carboxy, oxo,  $C_1-C_4$  alkyl,  $C_1-C_4$ -alkoxy,  $C_1-C_4$  alkanoyl, carbamoyl;

$X$  is independently a bond or  $C_1-C_4$  alkyl;

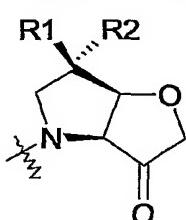
5  $Ra$  is independently H,  $C_1-C_4$  alkyl or  $CH_3C(=O)$ ;

$Rb$  is independently H, or  $C_1-C_4$  alkyl

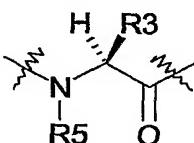
$m$  is independently 0,1 or 2;

or a pharmaceutically acceptable salt or prodrug thereof.

10 2. A compound according to claim 1, wherein the stereochemistry is as depicted in the partial structure below:



15 3. A compound according to claim 1, wherein the stereochemistry is as depicted in the partial structure below:



4. A compound according to claim 1, wherein  $R^2$  is halo and  $R^1$  is H.

5. A compound according to claim 4, wherein  $R^2$  is fluoro.

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6. A compound according to claim 1, wherein  $R^1$  and  $R^2$  are fluoro.

7. A compound according to claim 1, wherein  $R^3$  is  $C_1-C_4$  branched chain alkyl.

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8. A compound according to claim 7, wherein  $R^3$  is iso-butyl.

9. A compound according to claim 1, wherein R<sup>3</sup> and R<sup>4</sup> together define spirocycloalkyl.
10. A compound according to claim 9, wherein R<sup>3</sup> and R<sup>4</sup> together define  
5 spirocyclohexyl.
11. A compound according to claim 1, wherein R<sup>5</sup> is H.
12. A compound according to claim 1, wherein E is -C(=O)-.
- 10 13. A compound according to claim 1, wherein R<sup>6</sup> is substituted phenyl.
14. A compound according to claim 13, wherein the substituent comprises -NRaRb, -CH<sub>2</sub>NRaRb, -NRbR<sup>9</sup>, -NRbC<sub>1</sub>-C<sub>4</sub>alkylR<sup>9</sup>, C<sub>1</sub>-C<sub>4</sub> straight or branched alkyl or -O-R<sup>9</sup>.
- 15 15. A compound according to claim 14, wherein the substituent comprises -NH-CH<sub>2</sub>phenyl, -NHCH<sub>2</sub>pyridyl or -NH-phenyl, wherein each phenyl or pyridyl ring is substituted with C<sub>1</sub>-C<sub>4</sub>-alkyl, -NRaRb, -NRbR<sup>9</sup> or -NRbC<sub>1</sub>-C<sub>4</sub>alkylR<sup>9</sup>.
- 20 16. A compound according to claim 13, wherein the substituent comprises C<sub>3</sub>-C<sub>6</sub> cycloalkyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, pyranyl, thiopyranyl, furanyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, phenyl, any of which is optionally substituted with R<sup>10</sup>.
- 25 17. A compound according to claim 16, wherein the substituent is selected from indolinyl, pyranyl, thiopyranyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, any of which is optionally substituted with R<sup>10</sup>.
- 30 18. A compound according to claim 17, wherein the substituent is thiazolyl, 5-methyl-thiazolyl or thienyl, optionally substituted with R<sup>10</sup>.
19. A compound according to claim 18, wherein the substituent is thiazol-4-yl, 5-methylthiazol-4-yl or thien-2-yl, optionally substituted with R<sup>10</sup>.

20. A compound according to claim 18, wherein the thiazolyl, 5-methylthiazolyl or theinyl is substituted with morpholinyl, morpholinylmethyl-, piperidinyl, piperidinylmethyl-, piperazinyl, piperazinylmethyl, any of which is substituted with C<sub>1</sub>-C<sub>3</sub> alkyl, fluoro,

5 difluoro or C<sub>1</sub>-C<sub>3</sub> alkyl-O-C<sub>1</sub>-C<sub>3</sub>alkyl-.

21. A compound according to claim 20, wherein the substituent to the thiazolyl, 5-methylthiazolyl or thienyl is piperid-4-yl which is substituted with methyl, piperazinyl which is N-substituted with C<sub>1</sub>-C<sub>3</sub> alkyl or methyloxyethyl-, -or piperid-1-ylmethyl- which

10 is unsubstituted or 4-substituted with fluoro or di-fluoro.

22. A compound according to claim 13, wherein the substituent comprises a morpholine, piperidine or piperazine ring, optionally substituted with R<sup>10</sup>.

15 23. A compound according to claim 22 comprising piperid-4-yl or N-piperazinyl, N-substituted with Ra or piperidin-1-yl which is 4-substituted with -NRaRb.

24. A compound according to claim 1, wherein R<sup>6</sup> is optionally substituted: benzothiazol or benzofuryl or benzoxazolyl.

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25. A compound according to claim 24, wherein the substituent is -OR<sup>9</sup>, -OXR<sup>9</sup> , -NRbR<sup>9</sup> or -NRbXR<sup>9</sup>.

26. A compound according to claim 25, wherein R<sup>9</sup> is piperid-4-yl, piperazin-1-yl or 25 piperidin-1-yl or morpholino, any of which is substituted with C<sub>1</sub>-C<sub>3</sub> alkyl.

27. A compound according to claim 26, wherein the optional substituent to R<sup>6</sup> is N-morpholinylethyoxy, N-methylpiperid-4-yloxy, or N-methylmorpholin-3-ylmethyoxy.

30 28. A pharmaceutical composition comprising a compound as defined in any of claims 1 to 27 and a pharmaceutically acceptable carrier or diluent therefor.

29 Use of a compound as defined in any of claims 1-27 in the manufacture of a medicament for the treatment of disorders mediated by cathepsin K.

30 Use according to claim 29, wherein the disorder is selected from:

- 5 osteoporosis,
- gingival diseases such as gingivitis and periodontitis,
- Paget's disease,
- hypercalcaemia of malignancy
- metabolic bone disease
- 10 diseases characterised by excessive cartilage or matrix degradation, such as osteoarthritis and rheumatoid arthritis.
- bone cancers including neoplasia,
- pain.